Medical Image Registration
Intra-patient Registration of 4DCT Images of Chest using Elastix

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***Index Terms*—CT Imaging, Image Registration, Elastix, Multi Resolution Registration.**

I. Introduction

DIR or deformable image registration is a technique of calculating a volume element correspondence between images. It is important for a doctor to be able to quantify pathology progression, and DIR can provide such an assessment. By developing a comprehensive method for intra-patient CT image registration, it is possible to improve the efficiency and quality of the diagnostic procedure. However, for patient safety, DIR spatial accuracy performance must be systematically and objectively assessed. The usage of landmark point-pairs technique for accuracy evaluation is one way to address this challenge. This method can be used to analyze registration in relation to the underlying anatomy depicted in medical imaging.

For the purposes of this project 4DCT scans were provided in inhale and exhale phase and 300 landmark features corresponding to both phases which were used for assessment of the best registration parameters.

II. Materials and Methods

A. Data

The project consists of using 4DCT scans and their respective landmarks for evaluation of deformable image registration between inhale and exhale phase. For each of the CT scans exactly 300 landmarks were provided. The image dimensions and displacement in relation to the specified landmarks were varied in each example as can be seen from Table I.

A clear difference can be seen between inhale and exhale phase with respect to a pre-defined slice as seen from Figure 1.

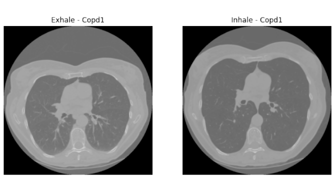

Fig. 1: Visual representation of a slice extracted with respect to axial view in case of COPD1 CT scene in exhale and inhale phase.

For the landmarks coordinates with respect to x,y and z axis a *'.txt'* file was provided which consisted of 300 rows corresponding to specific locations for aforementioned axis. For each file when observing the landmarks between the phases of inhale and exhale, the number of a specific row corresponded to a mutual landmark in the other phase.

B. Data Pre-processing

As can be observed in Figure 1, the images presented are visibly washed out, hence some form of pre-processing is required. Contrast Limited Adaptive Histogram Equalization, or CLAHE, was used specifically for image pre-processing.

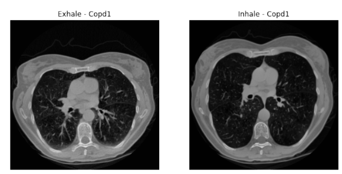

Fig. 2: Visual representation of a slice extracted with respect to axial view in case of COPD1 CT scene in exhale and inhale phase after applying CLAHE as a pre-processing technique

Notably from Figure 2, when applying CLEHE to the provided CT scans the borders for anatomical features become more distinct which is expected to improve results of registration.

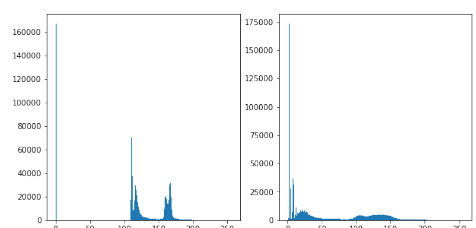

Fig. 3: Histogram of COPD1 CT scan before (left) and after (right) application of CLEHE

C. Image Registration

Image registration is a procedure of aligning two or multiple images to a predefined fixed frame. Through image registration a transformation matrix or deformation field is produced which is then used to map one image to the frame of the other. For image registration some of the base parameters which need to be considered for registration are images used and

Label	Image Dims	Voxels (mm)	# Features	Displacement (mm)	# Repeats	Observers (mm)
COPD1	512 x 512 x 121	0.625 x 0.625 x 2.5	773	25.90 (11.57)	150/3	0.65 (0.73)
COPD2	512 x 512 x 102	0.645 x 0.645 x 2.5	612	21.77 (6.46)	150/3	1.06 (1.51)
COPD3	512 x 512 x 126	0.652 x 0.652 x 2.5	1172	12.29 (6.39)	150/3	0.58 (0.87)
COPD4	512 x 512 x 126	0.590 x 0.590 x 2.5	786	30.90 (13.49)	150/3	0.71 (0.96)

TABLE I: Header information for each case of the provided CT scans.

additional information corresponding to physical coordinates, metric which quantifies the quality of alignment. In our case four different metrics were used Mutual Information, Mean Squared Difference, Normalised Correlation Coefficient, Normalized Mutual Information and the best one was chosen as the one which lead to best quantitative results with respect to TRE. The image sampler is the second crucial element in image registration, and it determines which areas in the image will be utilized to evaluate registration. In our case Random Coordinate sampler was used which is not limited to only voxel positions but also coordinates between voxels can be selected through usage of interpolation. For the sampler, only the number of spatial samples was optimized. For the aforementioned N-th order B-Spline function was used. For the transformation two types of transformations were used, B-Spline and Affine. However, affine was used solely in combination with B-Spline, whereas B-Spline was optimised on its own and also used as a seperete registration method. Optimizer of choise is another important element of registration as it estimates what are the optimal transform parameters and in this case only Adaptive Stochastic Gradient Descent was used with automatic parameters estimation set to true. Furthermore only the maximum number of iterations for the optimizer was customized. Another essential aspect of this registration was the employment of a multi-resolution strategy, in which lower-complexity images are first registered, and subsequently refined images are processed using the registration base of previously utilized images. The most important parameter modified with respect to this is image pyramid schedule.

1) B-Spline Registration

B-Spline image registration is a type of non-rigid image registration between the pre-defined moving and fixed images. With image registration a transformation matrix or deformation field is produced which spatially aligns moving image to the fixed image once the appropriate transformation has been applied. A uniform grid of control points defines the B-Spline nonrigid transformation, which is influenced by a variety of characteristics such as grid spacing between the corresponding nodes. The grid spacing effects the density and hence the locality of a transformation. The bigger the space between grid nodes the coarser the details are observed. Main two parameters optimized were final grid spacing in voxels and grid spacing schedule.

2) Affine Registration

Before implementing the non-rigid type of transformation, affine registration is frequently utilized as a starting point. For more complex transformations, it provides good initialization parameters. However, in this case application of affine registration was implemented after the b-spline parameters had been tuned. It's worth noting that, like the B-spline transformation, there are a plethora of potential parameter combinations. Especially when combining B-spline and affine implementation parameter tuning. That is why only some paramaeters have been tuned with respect to affine transformation and others were set following the B-spline parameters.

D. Evaluation Metric

For the evaluation of results, TRE or target registration error was calculated which quantifies the distance after registration between corresponding points. Furthermore, when calculating TRE the voxels dimensions had to be taken into consideration for each specific case.

$$TRE\,(i,e) = \sqrt{\sum_{i=1}^{n} \left(vox_{dim} * e_i - vox_{dim} * i_i\right)^2}$$

Where i corresponds to inhale landmark, e corresponds to exhale landmark and vox_{dim} correspond to the voxel dimensions as seen from Table I.

E. Implementation

Data visualization was done using SnapITK which enables navigation of three dimensional images. However for the landmarks, a provided MATLAB utility pack was used for visualization. It is important to note that when loading data into SnapITK it was required to reorient the image with respect to the Z axis, going from *Inferior to Superior* to *Superior to Inferior* and then save it again before doing the image registration.

For the data-preprocessing Python 3.7 was used in combination with nibabel 3.2.1 for loading the images and saving, numpy 1.21.2 and skimage 0.18.1. Skimage was used for application of CLEHE and nibabel was used for saving considering the header information with respect to voxel dimensions from the previously loaded nifti files. Once the images have been saved the reorientation of axis was required using SnapITK and saving again before doing image registration.

For Image Registration elastix 5.0.0 was used in Windows command prompt.

III. Optimization Process and Results

A. B-Spline Transform Parameter Tuning

To begin with image registration, there are a number of parameters to set up, thus an existing parameter script [3] was used and fine-tuned for the task at hand. The initial parameters can be seen on Table II.

The tuning of parameters procedure consisted in varying one variable whereas keeping others to constant in the order as they are presented in the Table II.

Number of Resolutions	3
Metric	AdvancedMattesMutualInformation
Number of Histogram Bins	32
Number of Spatial Samples	2000
Final Grid Spacing	12.0 12.0 12.0
Grid Spacing Schedule	1.0 1.0 1.0
Image Pyramid Schedule	Default
Maximum Number of Iterations	1000

TABLE II: Initial parameters used for B-Spline Transformation.

1) *Number of Resolutions*

The number of resolutions parameter was varied in range from 1 to 6. As can be seen in Table III, the best average TRE results were obtained with 6 resolutions, therefore that parameter was adjusted to 6 and utilized as such from then on. Furthermore, only in the instance of copd2 were the results were marginally worse than when utilizing 3, 4, or 5 resolutions, although the difference is minor when considering that the results were better in all other circumstances.

Number of Resolutins	copd1	copd2	copd3	copd4	Average TRE
3	23.296 (11.269)	19.715 (7.93)	10.88 (6.49)	27.85 (12.74)	20.43525
4	22.256(11.402)	19.047(8.438)	9.334(6.409)	26.724(12.458)	19.34025
5	20.024(11.913)	19.079(8.388)	7.909(5.572)	25.898(11.707)	18.2275
6	19.578(13.528)	19.716(7.757)	7.072(5.295)	23.612(12.730)	**17.4945**
7	18.588(12.268)	26.059(12.094)	12.005(7.931)	29.147(12.093)	21.4485

TABLE III: TRE for each one of the cases when varying number of resolutions in range from 1 to 6.

2) *Metric*

The metric that was used was the next important parameter that was tuned. In fact, the metric Mattes Mutual Information, which was first chosen, produced the best results. In the case of copd2, normalized mutual information lead to better results, however that wasn't the general trend as can be seen from Table IV. The metric was kept at *AdvancedMattesMutualInformation* from than on.

Number of Resolutins	copd1	copd2	copd3	copd4	Average TRE
AdvancedMattesMutualInformation	19.578(13.528)	19.716(7.757)	7.072(5.295)	23.612(12.730)	**17.4945**
AdvancedMeanSquares	28.56 (18.48)	22.54 (10.34)	12.85 (6.66)	37.13 (20.77)	25.27
AdvancedNormalizedCorrelation	24.46 (17.72)	24.03 (11.77)	12.77 (7.12)	32.58 (18.75)	23.46
NormalizedMutualInformation	19.74 (13.93)	19.27 (7.87)	7.17 (5.27)	23.86 (12.9)	17.51

TABLE IV: TRE for each one of the cases when varying the metric used.

3) *Number of Histogram Bins*

While adjusting the number of histogram bins and setting them to values of 16, 32, and 64, the best results were obtained when utilizing the starting parameter of 32 as can be seen from Table V.

Number of Hisrogram Bins	copd1	copd2	copd3	copd4	Average TRE
16	21.270(14.429)	23.432(11.432)	12.573(8.218)	27.970(16.725)	21.31125
32	19.578(13.528)	19.716(7.757)	7.072(5.295)	23.612(12.730)	**17.4945**
64	20.398(11.497)	18.388(7.444)	7.716(5.387)	25.267(12.511)	17.94225

TABLE V: TRE for each one of the cases when varying the number of histogram bins.

4) *Number of Spatial Samples*

Number of spatial samples was varied in range from 1000-1000, specifically 4 values were sampled, 1000, 2000, 5000 and 10000. Best results were achieved when setting the number of spatial samples to 5000 as seen from Table VI.

Number of Spatial Samples	copd1	copd2	copd3	copd4	Average TRE
1000	19.458(12.528)	18.874(7.491)	7.62(5.065)	23.845(13.056)	17.44925
2000	19.578(13.528)	19.716(7.757)	7.072(5.295)	23.612(12.730)	17.4945
5000	19.530(13.443)	20.142(8.467)	6.619(5.496)	23.207(12.350)	17.3745
10000	19.645(13.339)	20.649(8.794)	6.450(5.667)	22.976(11.824)	17.43

TABLE VI: TRE for each one of the cases when varying the number spatial samples.

5) *Final Grid Spacing and Grid Spacing Schedule*

These two parameters were the only ones that were modified concurrently where for every value of final grid spacing a number of pre-defined grid spacing schedules was used. Although the first strategy was to establish final grid spacing first, then grid spacing schedule, after a brief experiment with combining the two parameters, it was determined that this was the superior way to achieve better outcomes. From the Table IX it can be concluded that the best results are achieved when using final grid spacing of 20.0 20.0 20.0 and grid spacing schedule of 8.0 4.0 2.0 1.0 1.0 1.0. It is important to note that these are just some of possible combination and their number increases by a great amount by just introducing one more value.

6) *Image Pyramid Schedule*

The next parameter that was changed was the Image Pyramid Schedule, but the final pyramid schedule was left to default. We believe the results in Table VII are as they are given that other parameters were optimized with the pyramid schedule set as default.

Image Pyramid Schedule	copd1	copd2	copd3	copd4	Average TRE
16.0 16.0 8.0 4.0 2.0 1.0	5.06 (4.74)	8.14 (7.702)	3.013 (2.74)	8.887 (6.11)	6.275
16.0 8.0 8.0 4.0 2.0 1.0	5.178 (4.683)	7.802 (7.25)	3.08 (2.74)	8.836 (6.12)	6.224
16.0 8.0 4.0 2.0 1.0 1.0	5.146 (4.82)	9.371 (6.84)	3.102 (2.823)	8.768 (6.03)	6.59675
8.0 8.0 4.0 2.0 1.0 1.0	4.898 (4.494)	9.564 (6.751)	3.122 (.2.853)	9.22 (6.40)	6.701
Default	5.126(4.847)	7.872(7.461)	3.006(2.726)	8.411(5.805)	**6.10375**

TABLE VII: TRE for each one of the cases when varying the number of histogram bins.

7) *Number of Iterations*

Maximum Number of Iterations	copd1	copd2	copd3	copd4	Average TRE
1000	5.126(4.847)	7.872(7.461)	3.006(2.726)	8.411(5.805)	6.10375
5000	4.556 (4.718)	7.32 (765)	2.88 (2.738)	8.44 (6.145)	5.799
10000	4.374 (4.63)	7.455 (8.01)	2.85 (2.704)	8.44 (6.342)	5.77975

TABLE VIII: TRE for each one of the cases when varying the maximum number of iterations.

Initially number of iterations was set to 1000 so to be able to smoothly run the code without much time consumption. Number of Iterations was varied, taking on values 1000, 5000 and 10000. Furthermore in case of number of iterations of 1000 the time it took was around 1 minute, for number of iterations of 5000 it took around 2 minutes and for 10000 it took around 5 minutes to run the code. In the end the decision was made to keep the number of iterations to 5000 given that they did increase in comparison to 1000 while the difference between setting the number of iterations 5000 or 10000 was negligible as seen from Table VIII.

Final Grid Spacing	Grid Spacing Schedule	copd1	copd2	copd3	copd4	Average TRE
50.0 50.0 50.0	4.0 2.0 1.0 1.0 1.0 1.0	7.132(4.686)	10.587(6.332)	4.733(3.0909)	10.386(6.821)	8.2095
50.0 50.0 50.0	8.0 4.0 2.0 1.0 1.0 1.0	7.069(4.694)	11.807(5.772)	4.932(3.283)	10.724(5.603)	8.633
50.0 50.0 50.0	16.0 8.0 4.0 2.0 1.0 1.0	7.121(4.990)	13.829(5.813)	5.141(3.504)	10.603(4.934)	9.1735
30.0 30.0 30.0	4.0 2.0 1.0 1.0 1.0 1.0	6.1709(5.071)	8.847(7.123)	3.729(3.035)	9.325(5.556)	7.017975
30.0 30.0 30.0	8.0 4.0 2.0 1.0 1.0 1.0	6.331(5.121)	9.829(6.529)	3.795(3.045)	9.001(5.547)	7.239
30.0 30.0 30.0	16.0 8.0 4.0 2.0 1.0 1.0	8.82 (6.47)	14.038 (5.895)	4.646 (3.562)	9.861 (4.865)	9.34125
20.0 20.0 20.0	4.0 2.0 1.0 1.0 1.0 1.0	6.69 (6.25)	14.277 (8.595)	3.793 (3.223)	11.179 (5.911)	8.98475
20.0 20.0 20.0	8.0 4.0 2.0 1.0 1.0 1.0	5.126(4.847)	7.872(7.461)	3.006(2.726)	8.411(5.805)	**6.10375**
20.0 20.0 20.0	16.0 8.0 4.0 2.0 1.0 1.0	5.352(4.812)	9.453(6.752)	3.272(2.894)	8.253(5.714)	6.5825

TABLE IX: TRE for each one of the cases when varying the final grid spacing and grid spacing schedule.

B. Affine Transform Parameters Tuning

After setting up the parameters for B-spline transformation, the next step was to investigate if adding affine transformation as initialization may improve the results even more. As previously said, the number of available parameters that can be adjusted is huge, thus only a few parameters were specified to be modified in advance. Those parameters include number of resolutions, metric, number of histogram bins, number of spatial samples and number of iterations.

The optimization procedure can be seen in table of Appendix. Furthermore from the table it can be seen that the overall average TRE dropped when introducing affine trasnformation before applying the B-spline transformation. The final average TRE is 5.534.

Final parameters used for affine transformation can be seen in Table X.

Number of Resolutions	6
Metric	AdvancedNormalizedCorrelation
Number of Histogram Bins	32
Number of Spatial Samples	2000
Maximum Number of Iterations	2000

TABLE X: Final parameters used for Affine Transformation.

IV. Final model Results and Discussion

The final combination of parameters used for image registration included following parameters for affine transformation:

- Number of Resolution was set to 6
- Metric used for Advanced Normalized Correlation
- Number of Histogram Bins was set to 32
- Number of Spatial Samples was set to 2000
- Maximum Number of Iterations was set to 2000

The affine transformation was followed by B-spline transformation and following final parameters for B-spline transformation were used:

- Number of Resolutions was set to 6
- Metric used for Advanced Mattes Mutual Information
- Number of Histogram bins was set to 32
- Number of Spatial Samples used for metric evaluation was 5000
- Final Grid Spacing was set to 20.0 20.0 20.0
- Grid Spacing Schedule was set to 8.0 4.0 2.0 1.0 1.0 1.0
- Image Pyramid Schedule was set to default
- Number of Iterations was set to 5000

By using these parameters an average TRE of 5.534 was achieved. For copd1 resulting TRE is 4.703, for copd2 it is 7.78, for copd3 is 3.04 and for copd4 is 6.613.

Furthermore qualitative analysis of results included observing image before and after registration. The visual consequences of integrating the two registrations are shown in Figure 4-7. These results show that while affine registration can produce good results on its own, attaining results that incorporate transformations in finer details necessitates combining the two registration methods.

Taking into consideration the qualitative and quantitative analysis it can be concluded that the less obstructed the volume is with information such as presence of other non-lung anatomy better results will be achieved. When comparing visually, copd1 and copd3 have much less non-lung information and the TRE achieved is better, whereas copd2 and copd4 are obstructed with more non-lung information, especially copd2.

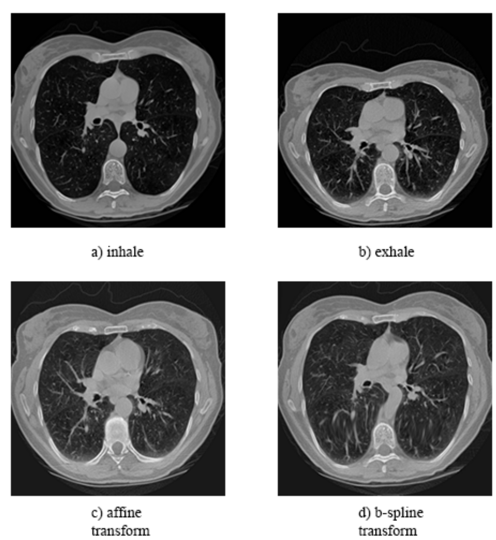

Fig. 4: Results of image registration for COPD1 in case of slice x = 93, y = 228 and z = 64.

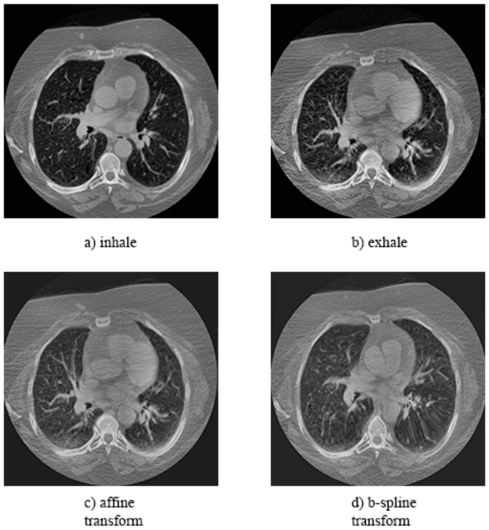

Fig. 5: Results of image registration for COPD2 in case of slice x = 93, y = 228 and z = 64.

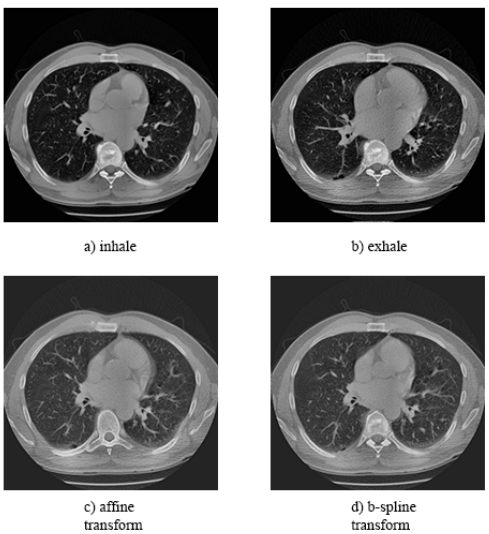

Fig. 6: Results of image registration for COPD3 in case of slice x = 93, y = 228 and z = 64.

V. Conclusion

- From the results, we can conclude that non rigid registration that uses B-spline curves can be an accurate and robust method for chest CT scan inhale-exhale registration when having a good parameters combination.
- Applying only affine transformation gives an acceptable registration, however for a non rigid transformation is needed to map the shape transformation in lungs between exhale and inhale phases.
- Including the Affine transformation as an initial step to the registration, increases the performance of the deformable registration.
- Registration parameters are dependent on one another, thus parameters optimization is a hard task to achieve, and results can be improved if additional combinations are investigated.

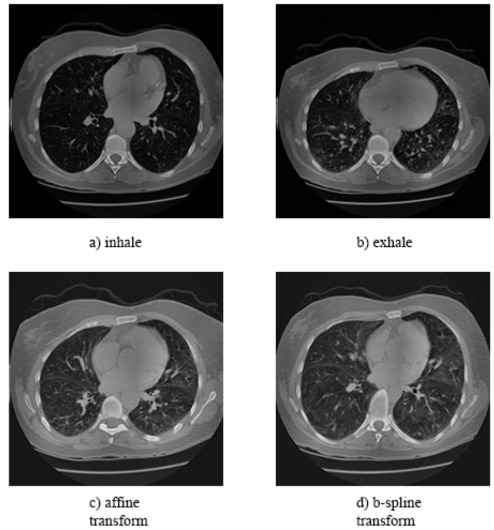

Fig. 7: Results of image registration for COPD4 in case of slice x = 93, y = 228 and z = 64.

- Preprocessing the image using CLAHE improves the registration, as the images are enhanced and region of interest is reduced.
- In addition to the work done, lung segmentation might be a helpful prepossessing step for image registration.

VI. Organization and development of the coursework

The project required a preliminary research of the overall concept of deformable image registration in the lungs, as well as the metric employed. Furthermore, the target registration error had to be implemented, and the evaluation metric's correctness was confirmed by comparing it to expected TRE provided online.

Other types of prepossessing techniques were evaluated such as Histogram equalization, Adaptative Histogram equalization, Histogram matching and intensity normalization. This part took us several days to choose the prepossessing used in the final pipeline.

Choosing the best preprocessing technique was dependent on the choice of the base parameter files for the registration. The choice was made to use available scripts from the elastix zoo repository on github.

The longest portion of the process was optimizing the parameters. An in-depth analysis of the elastix manual was performed, and one-by-one parameter optimization was implemented. First, the B-spline transformation was used since we thought that because it is a non-rigid transformation, it would produce superior results. Following that, the decision was made to try and incorporate and optimize affine transformation. The concept was that an affine transformation may serve as a good foundation for a B-spline transformation. This was the most time-consuming aspect of the project.

REFERENCES

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[3] https://elastix.lumc.nl/modelzoo/par0003/

APPENDIX

Affine Transformation Parameter Fine-Tuninig

Number of Resolutions	Metric	Number of Histogram Bins	Number of Spatial Samples	Maximum Number of Iterations	copd1	copd2	copd3	copd4	Average TRE
3	AdvancedMattesMutualInformation	32	1000	1000	11.69 (5.224)	7.898 (7.33)	3.08 (2.735)	7.97 (5.47)	7.6595
4					4.809 (4.543)	7.937 (7.316)	3.04 (2.664)	7.67 (5.322)	5.864
5					4.747 (4.497)	7.916 (7.275)	3.04 (2.679)	6.882 (5.132)	5.64625
6					4.698 (4.484)	8.069 (7.328)	3.05 (2.669)	6.67 (4.96)	5.62175
7					4.705 (4.476)	8.103 (7.34)	3.03 (2.675)	6.66 (4.897)	5.6245
	AdvancedMattesMutualInformation				4.698 (4.484)	8.069 (7.328)	3.05 (2.669)	6.67 (4.96)	5.62175
	AdvancedMeanSquares				4.727 (4.534)	7.856 (7.27)	3.04 (2.67)	6.66 (5.0)	5.57075
	AdvancedNormalizedCorrelation				4.729 (4.487)	7.857 (7.253)	3.02 (2.67)	6.628 (4.94)	5.5585
	NormalizedMutualInformation				4.692 (4.494)	8.028 (7.351)	3.03 (2.68)	6.67 (4.95)	5.605
		16			Doesn't Change				
		32			4.729 (4.487)	7.857 (7.253)	3.02 (2.67)	6.628 (4.94)	5.5585
		64			Doesn't Change				
			1000		4.729 (4.487)	7.857 (7.253)	3.02 (2.67)	6.628 (4.94)	5.5585
			2000		4.74 (4.524)	7.803 (7.28)	3.03 (2.68)	6.620 (4.93)	5.54825
			5000		4.76 (4.508)	7.84 (7.25)	3.03 (2.67)	6.64 (4.92)	5.5675
				2000	4.703 (4.492)	7.78 (7.285)	3.04 (2.654)	6.613 (4.92)	5.534
				5000	4.727 (4.50)	7.777 (7.252)	3.04 (2.677)	6.63 (4.913)	5.5435